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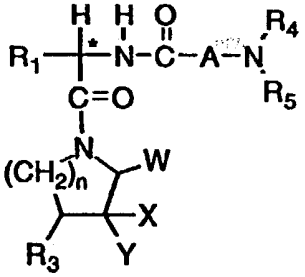
(54) Title: PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE

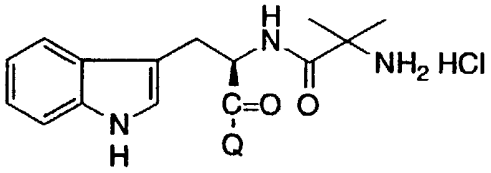
(57) Abstract

The present invention is directed to certain piperidine, pyrrolidine, and hexahydro-1H-azepine compounds of general structural formula (I) wherein R_1, R_3, R_4, R_5, A, W, X, Y, and n are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such compounds as the active ingredient thereof are also disclosed.

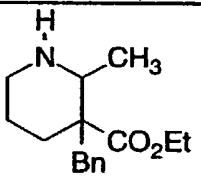
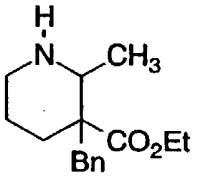
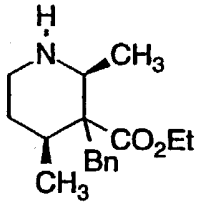


(I)

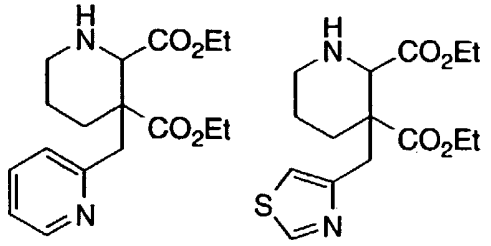
TABLE AIV: ADDITIONAL EXAMPLES



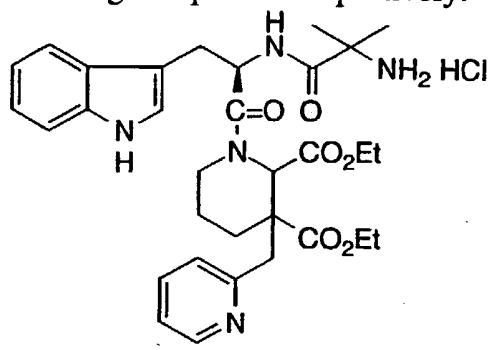
Product

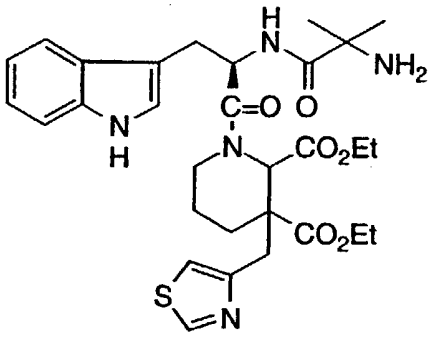
	Intermediate (QH)	Product
entry	MF FAB-MS (M+1)	MF FAB-MS (M+1)
1		d1: $C_{31}H_{40}N_4O_4$ 533
2		d2: $C_{31}H_{40}N_4O_4$ 533
3		mixture of diastereomers $C_{32}H_{42}N_4O_4$ 547

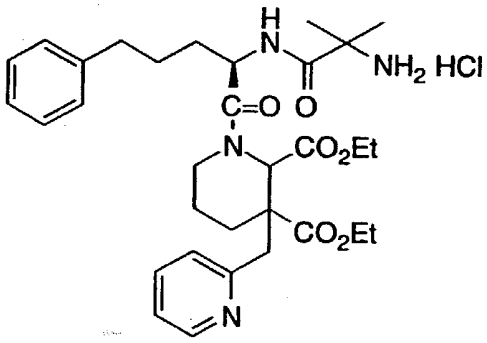
Likewise the compounds shown below are prepared according to Example A12 by alkylating with 2-picolyl chloride or 4-bromomethylthiazole to give the following intermediates:

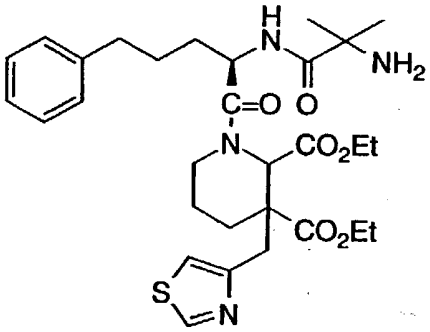


which may then be reacted with Intermediates 1 or 2 to give the following compounds respectively:

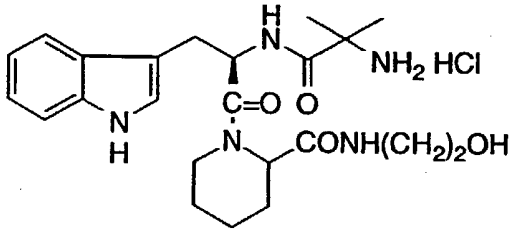




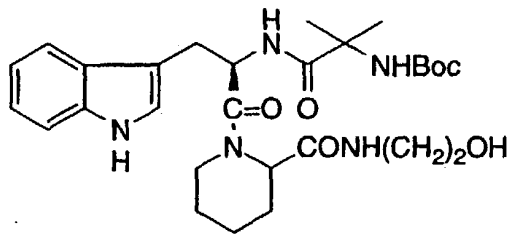




EXAMPLE A13



Step A:



To a stirred solution of dl-2-pipecolamidoethanol (100 mg, (1.16 mmol), HOBT (78.38 mg, 1.16 mmol) and Intermediate 1 (226.12 mg, 1.16 mmol) in dichloromethane (3ml) at ambient temperature was added 4-methyl morpholine (63.8 ml, (1.16 mmol). The mixture was cooled to 0° C and to which was added EDC (222.3 mg, 2.32 mmol). The reaction mixture was stirred at room temperature for 16 h. After evaporation, the residue was partitioned in ethyl acetate and 1N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered, and evaporated to an oily foam which was purified by preparative tlc (acetone/chloroform: 3/7) to give 91 mg of the product (R_f= 0.45).
CI-MS : calc. for $C_{28}H_{41}N_5O_6$: 543 ; Found 544(M+H)
^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (br.s, 1H), 7.57 & 7.55 (2s, 1H),7.35, 7.33, (2s, 2H), 7.17 (t, J= 6.95Hz, 1H), 7.15-7.07 (m, 3H), 7.03 (distorted t, J= 4.95 Hz, 1H), 5.16 (d, J=4.68 Hz, 1H), 4.94 (m, 2H), 3.65 (m, 2H), 3.55-3.10 (m, 5H), 2.9-2.62 (m, 4H), 2.3-2.2 (m, 1H), 1.43, 1.46 and 1.41 (3 s, total 15H), 1.00 (m, 1H), 0.83 (m, 1H).

Step B: